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MOLECULAR BIOLOGY OF THE CELL

**Bruce Alberts • Dennis Bray
Julian Lewis • Martin Raff • Keith Roberts
James D. Watson**



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"Long ago it became evident that the key to every biological problem must finally be sought in the cell, for every living organism is, or at sometime has been, a cell."

Edmund B. Wilson
The Cell in Development and Heredity
3rd edition, 1925, Macmillan, Inc.

Bruce Alberts received his Ph.D. from Harvard University and is currently a Professor in the Department of Biochemistry and Biophysics at the University of California Medical School in San Francisco. Dennis Bray received his Ph.D. from the Massachusetts Institute of Technology and is currently a Senior Scientist in the Medical Research Council Cell Biophysics Unit at King's College London. Julian Lewis received his D.Phil. from Oxford University and is currently a Lecturer in the Anatomy Department at King's College London. Martin Raff received his M.D. degree from McGill University and is currently a Professor in the Zoology Department at University College London. Keith Roberts received his Ph.D. from Cambridge University and is currently Head of the Department of Cell Biology at the John Innes Institute, Norwich. James D. Watson received his Ph.D. from the University of Indiana and is currently Director of the Cold Spring Harbor Laboratory. He is the author of *Molecular Biology of the Gene* and, with Francis Crick and Maurice Wilkins, won the Nobel Prize in Medicine and Physiology in 1962.

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Summary

The plasma membranes of neighboring cells in tissues are linked to each other at specialized contact sites called cell junctions. Three main types of cell junctions occur in most vertebrate tissues: desmosomes, tight junctions, and gap junctions. Desmosomes mechanically hold cells together—either at buttonlike points of contact (spot desmosomes) or at continuous bands of contact around interacting cells in an epithelial sheet (belt desmosomes). Both types of desmosomes serve in different ways as anchorage sites for components of the cell cytoskeleton. Tight junctions play an indirect but critical part in the transport of small hydrophilic molecules across epithelial cell sheets. They do so in two ways: they seal the plasma membranes of adjacent cells together so that even small molecules cannot leak between them, and they serve as diffusion barriers within each lipid bilayer so that specific transport proteins can be restricted to the apical or the basolateral compartments of the epithelial cell plasma membrane. Gap junctions are thought to be composed of clusters of protein channels that allow ions and molecules of less than about 1500 daltons to pass directly from the inside of one cell to the inside of the other. Cells connected by gap junctions share many of their small molecules and are said to be metabolically and ionically (electrically) coupled. While gap junctions are clearly important in coordinating the activities of electrically active cells, it is still unclear why so many other types of cells are coupled to each other by gap junctions.

* The Extracellular Matrix¹²

Most cells in multicellular organisms are in contact with an intricate meshwork of interacting, extracellular macromolecules that constitute the **extracellular matrix** (Figure 12-37). These versatile protein and polysaccharide molecules are secreted locally and assemble into an organized meshwork in the extracellular space of most tissues. In addition to serving as a universal biological glue, they also form highly specialized structures such as cartilage, tendons, basal laminae, and (with the secondary deposition of a form of calcium phosphate crystals) bone and teeth. While we shall confine our discussion to the extracellular matrix of vertebrates, unique and interesting related structures are seen in many other organisms, such as the cell walls of bacteria and plants, the cuticles of worms and insects, and the shells of mollusks.

Until recently, the vertebrate extracellular matrix was thought to serve mainly as a relatively inert scaffolding that stabilized the physical structure of tissues. But now it is clear that the matrix plays a far more active and complex role in regulating the behavior of the cells that contact it—influencing their development, migration, proliferation, shape, and metabolic functions. The extracellular matrix has a correspondingly complex molecular composition; unfortunately our understanding of its organization is still fragmentary.

* The Extracellular Matrix Consists Primarily of Fibrous Proteins Embedded in a Hydrated Polysaccharide Gel

The macromolecules that constitute the extracellular matrix are secreted by local cells, especially fibroblasts, which are widely distributed in the matrix. In specialized matrix structures, such as cartilage and bone, these macromolecules are secreted locally by more specialized cells: for example, chondroblasts form cartilage, and osteoblasts form bone. Two of the main classes of extracellular macromolecules that make up the matrix are (1) the collagens

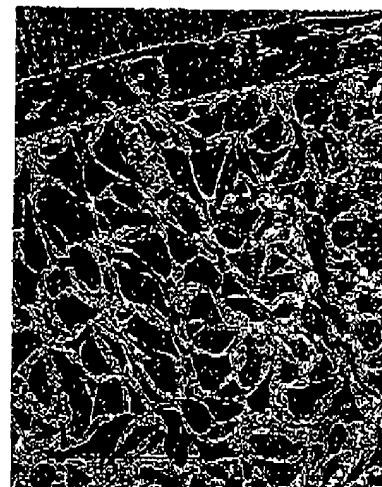


Figure 12-37 Low-power electron micrograph showing cells surrounded by spaces filled with extracellular matrix. The particular cells shown are those in an early chick limb during the time when different cell characters are being determined. (Courtesy of Cheryll Tickle.)

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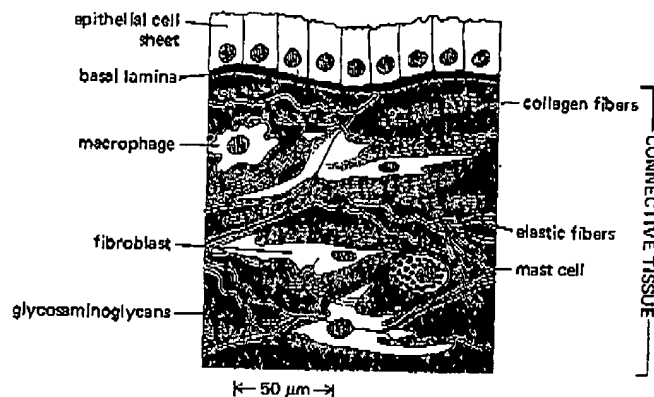


Figure 12-38 Schematic drawing of the connective tissue underlying an epithelial cell sheet.

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and (2) the polysaccharide glycosaminoglycans (GAGs), which are usually covalently linked to protein to form proteoglycans. The glycosaminoglycan and proteoglycan molecules form a highly hydrated, gel-like "ground substance" in which collagen fibers are embedded. While the long collagen fibers strengthen and help to organize the matrix, the aqueous phase of the polysaccharide gel permits the diffusion of nutrients, metabolites, and hormones between the blood and the tissue cells. In many cases, fibers of the rubberlike protein elastin are also present and impart resilience to the matrix. In addition, two high molecular weight glycoproteins are among the major components of extracellular matrices: fibronectin, which is widely distributed in connective tissues (as well as in the blood), and laminin, which has so far been found only in basal laminae. Many other protein components of this type no doubt remain to be discovered.

The term **connective tissue** is often used to describe the extracellular matrix plus the cells found in it, such as fibroblasts, macrophages, and mast cells (Figures 12-38 and 12-39). The amount of connective tissue in organs varies greatly: skin and bone are composed mainly of connective tissue, whereas the brain and spinal cord contain very little. Moreover, the relative amounts of the different types of matrix macromolecules and the way that they are organized within the extracellular matrix vary enormously, giving rise to an amazing diversity of forms, each highly adapted to the functional requirements of the particular tissue. Thus, the matrix can become calcified to form the rock-hard structures of bone or teeth, or it can assume an almost crystalline order to form the transparent matrix of the cornea (the anterior covering of the eye), or it may take on the ropelike organization of the collagen fibers in tendons, which gives them their enormous tensile strength.

Collagen Is the Major Protein of the Extracellular Matrix¹²

The **collagens** are a family of highly characteristic fibrous proteins found in all multicellular animals. They are the most abundant proteins in mammals, constituting 25% of their total protein. The central feature of all collagen molecules is their stiff, triple-stranded helical structure. Three collagen polypeptide chains, called α -chains, are wound around each other in a regular helix to generate a ropelike collagen molecule about 300 nm long and 1.5 nm in diameter (Figure 12-40).

So far, seven genetically distinct collagen α -chains, each about 1000 amino acid residues long, have been well defined (Table 12-2). Although in principle more than 100 different types of triple-stranded collagen molecules could be assembled from various combinations of these seven α -chains, fewer than a

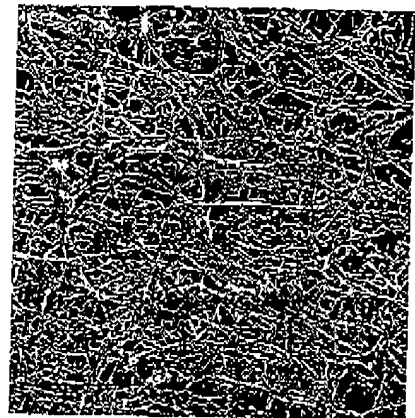


Figure 12-39 Scanning electron micrograph of fibroblasts (arrows) in the extracellular matrix of the cornea in a chick embryo. The matrix is largely composed of collagen fibrils (there are no elastic fibers in the cornea). The glycosaminoglycans, which normally form a hydrated gel filling the interstices of the fibrous network, have collapsed onto the surface of the collagen fibers during the dehydration process involved in specimen preparation. (Courtesy of Robert Trelstad.)

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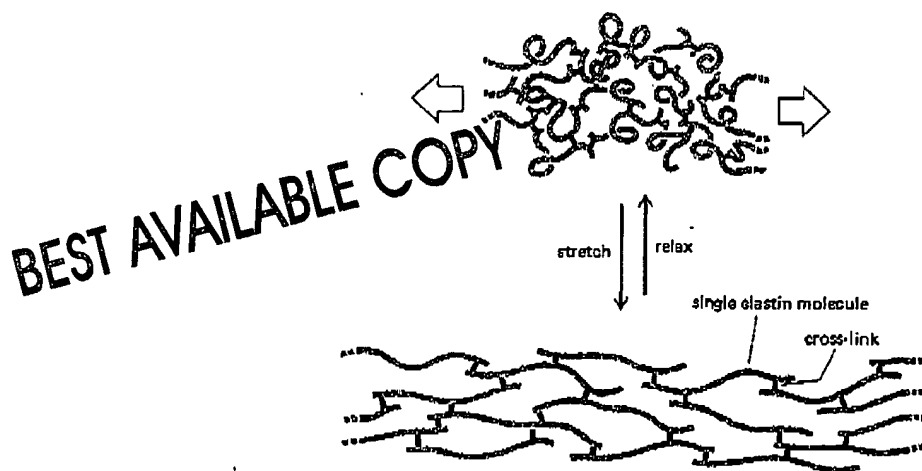


Figure 12-53 Elastin molecules are joined together by covalent bonds to generate an extensive cross-linked network. Because each elastin molecule in the network can expand and contract as a random coil, the entire network can stretch and recoil like a rubber band.

Elastic fibers are not composed solely of elastin, however; they also contain a glycoprotein that is usually distributed as microfibrils on the surface of the elastic fibers. In developing elastic tissues, these glycoprotein microfibrils often appear before elastin does and may serve to organize the secreted elastin molecules into the fibers and sheets which they later form.

* Proteoglycans and Hyaluronic Acid Are Major Constituents of the Extracellular Matrix¹⁶

Glycosaminoglycans (GAGs), formerly known as mucopolysaccharides, are long, unbranched polysaccharide chains composed of repeating disaccharide units. They are now called glycosaminoglycans because one of the two sugar residues in the repeating disaccharide is always an amino sugar (*N*-acetylglucosamine or *N*-acetylgalactosamine). Glycosaminoglycans are highly negatively charged due to the presence of sulfate or carboxyl groups or both on many of the sugar residues (Figure 12-54). Seven groups of glycosaminoglycans have been distinguished by their sugar residues, the type of linkage between these residues, and the number and location of sulfate groups. They are *hyaluronic acid* (the only group in which none of the sugars is sulfated), *chondroitin 4-sulfate*, *chondroitin 6-sulfate*, *dermatan sulfate*, *heparan sulfate*, *heparin*, and *keratan sulfate* (Table 12-3).

Hyaluronic acid (also called hyaluronate) exists as a single, very long carbohydrate chain of several thousand sugar residues in a regular, repeating

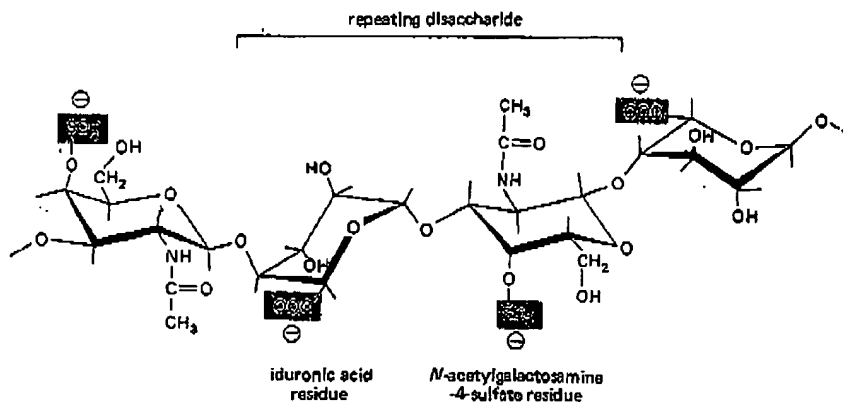


Figure 12-54 A repeating disaccharide sequence of the glycosaminoglycan chain of a dermatan sulfate molecule. Note the high density of negative charges along the chain due to the presence of both carboxyl and sulfate groups.